Claims

1. A pharmaceutical composition for treatment and/or p revention of a disease due to constriction or vasodilation of blood vessels, which comprises an EDG-5 modulator.

2. The pharmaceutical composition for treatment and/or prevention of a disease according to claim 1, wherein the disease due to constriction or vasodilation of blood vessels is selected from cerebrovascular spasmodic disorder, cardiovasucular spasmodic disorder, hypertension, renal disease, cardiac infarction, cardiac angina, arrhythmia, facilitation of the portal blood pressure, varicosity, chronic headache, haemorrhoid and congestive disorder.

3. The pharmaceutical composition for treatment and/or prevention of a disease according to claim 2, wherein the blood vessel is cerebral artery, renal artery, coronary artery, pulmonary artery, aorta and vein.

4. The pharmaceutical composition for treatment and/or prevention of a disease due to constriction of blood vessels according to claim 1, wherein the EDG-5 modulator is an EDG-5 antagonist.

5. The pharmaceutical composition for treatment a nd/or prevention of a disease according to claim 4, wherein the disease due to constriction of blood vessels is cerebrovascular spasmodic disorder, cardiovasucular spasmodic disorder, hypertension, renal disease, cardiac infarction, cardiac angina, arrhythmia, facilitation of the portal blood pressure, varicosity, chronic headache, haemorrhoid and congestive disorder.

6. The pharmaceutical composition for treatment and/or prevention of a disease due to constriction of blood vessels according to claim 4, wherein the EDG-5 antagonist is a compound represented by formula (I):

A—X—Y—Z—B (I)

wherein A represents cyclic group optionally with a substituent(s),

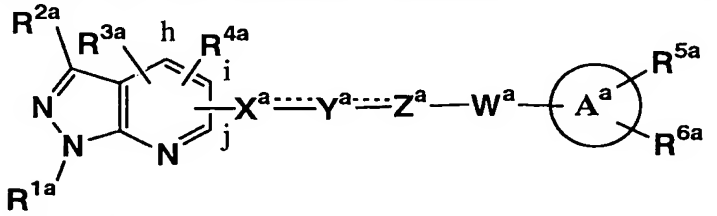
X represents a single bond or a spacer of principal chain atomicities which are 1-3,

Y represents a single bond or a spacer of principal chain atomicities which are 1-3,

Z represents a single bond or a spacer of principal chain atomicities which are 1-3, and

B represents cyclic group optionally with a substituent(s), or
a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition for treatment and/or prevention of a disease due to constriction of blood vessels according to claim 4, wherein the EDG-5 antagonist is a pyrazolopyridine compound represented b y formula (II):



(II)

wherein R^{1a} represents hydrogen; C1-8 alkyl; or $-COR^{7a}$, wherein R^{7a} represents C1-8 alkyl, optionally substituted aryl, optionally substituted aralkyl, C1 -6 alkoxy, optionally substituted aryloxy or optio nally substituted aralkyloxy;

R^{2a} represents C1-8 alkyl or optionally substituted aryl;

R^{3a} represents hydrogen, C1-8 alkyl, C1-6 alkoxy, C2-6 alkoxycarbonyl, haloalkyl, C3-7 cycloalkyl or optionally substituted aryl;

R^{4a} represents hydrogen or C1-8 alkyl;

R^{5a} and R^{6a}, each independently, represents hydrogen, C1-8 alkyl, C1-6 alkoxy, C2-6 alkoxycarbonyl, carboxyl, C2-6 alkynyl, halogen, cyano, nitro, haloalkyl, C1 -8 alkylamino, di(C1-8 alkyl)amino, acyl, hydroxy, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted aryl, optionally substituted aralkyl, alkoxyalkyl or $-CONHR^{8a}$, wherein R^{8a} represents optionally substituted aryl or optionally substituted aralkyl);

X^a represents $-N(R^{9a})-$, wherein R^{9a} represents hydrogen, C1-8 alkyl or $-NHR^{10a}$, wherein R^{10a} represents carboxyl or C2-6 alkoxycarbonyl; -O-; -N=; -CH=; or $-CH(R^{11a})-$, wherein R^{11a} represents hydrogen or C1-8 alkyl;

Y^a represents $-N(R^{12a})-$, wherein R^{12a} represents hydrogen, C1-8 alkyl, optionally substituted aralkyl, C2-6 alkoxycarbonyl, optionally substituted aryloxycarbonyl, optionally substituted aralkyloxycarbonyl or $-CONHR^{13a}$, wherein R^{13a} represents optionally substituted aryl or optionally substituted aralkyl ; =N-; $-CH_2-$; =CH-; -O-; -CO-; or a single bond;

Z^a represents -CO-, -CS-, $-CH_2-$, -O- or a single bond;

W^a represents $-N(R^{14a})-$, wherein R^{14a} represents hydrogen, C1-8 alkyl, optionally substituted aralkyloxycarbonyl, optionally substituted aryloxycarbonyl or heteroaryl-C1-8 alkyl; -O-; -CO-; -CONH-, wherein the nitrogen atom binds to ringA^a; $-CH_2-$; $-NHCH_2-$, wherein the carbon atom binds to ringA^a; or a single bond; and

represents double bond or single bond;

RingA^a represents optionally substituted aryl, heteroaryl or C3-7 cycloalkyl, or a nontoxic salt thereof.

8. The pharmaceutical composition for treatment and/or prevention of a disease due to constriction of blood vessels according to claim 1, wherein the EDG-5 modulator is an EDG-5 agonist.

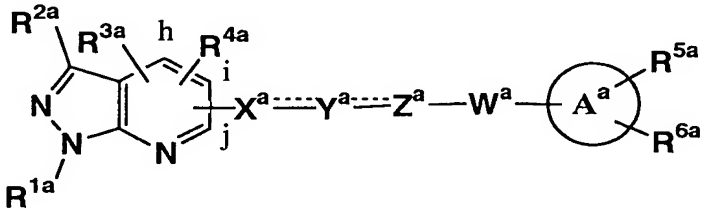
9. The pharmaceutical composition for treatment and/or prevention of a disease according to claim 8, wherein the disease due to vasodilation of blood vessels is chronic headache, haemorrhoid or congestive disorder.

10. A compound represented by formula (I):

A—X—Y—Z—B (I)

wherein all the symbols have the same meanings as those of claim 6, or a pharmaceutically acceptable salt thereof.

11. A compound represented by formula (I) according to claim 10, or a pharmaceutically acceptable salt thereof, which excludes a compound represented by formula (II):



(II)

wherein all the symbols have the same meanings as those of claim 7, a nontoxic salt thereof, 4-(4-chlorophenyl)-N-(3-(2-(diisopropylamino)ethoxy)-4-methoxyphenyl)-4-hydroxy-1-piperidinecarboxamide, N-(3-chlorophenyl)-4-(4-chlorophenyl)-4-hydroxy-1-piperidinecarboxamide, 4-(4-chlorophenyl)-N-(3,4-dichlorophenyl)-4-hydroxy-1-piperidinecarboxamide, methyl-2-(benzyloxy)-5-(((4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)carbonyl)amino)benzoate, 4-(4-bromophenyl)-N-(4-chlorophenyl)-4-hydroxy-1-piperidinecarboxamide, 4-(4-bromophenyl)-4-hydroxy-N-(3-trifluoromethyl)phenyl)-1-piperidinecarboxamide, and 4-(4-bromophenyl)-4-hydroxy-N-phenyl-1-piperidinecarboxamide.

12. The compound according to claim 11, wherein X is a single bond.

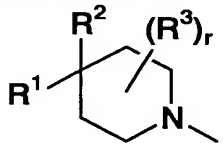
13. The compound according to claim 12, wherein Y is -CO- or -CS-.

14. The compound according to claim 13, wherein Z is -NH-.

15. The compound according to claim 14, wherein the cyclic group optionally with a substituent(s) represented by A is an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

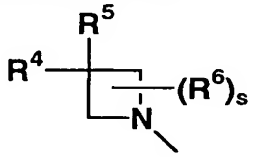
16. The compound according to claim 14, wherein the cyclic group optionally with a substituent(s) represented by A is an optionally saturated or unsaturated 4-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

17. The compound according to claim 15, wherein the cyclic group optionally with a substituent(s) represented by A is



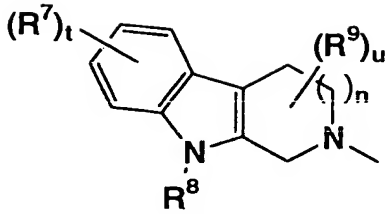
wherein R^1 represents a substituent,
R^2 represents hydrogen, hydroxy, or C1-6 alkoky,
R^3 represents a substituent, and
r represents 0 or an integer of 1-4.

18. The compound according to claim 15, wherein the cyclic group optionally with a substituent(s) represented by A is



wherein R^4 represents a substituent,
R^5 represents hydrogen, hydroxy, or C1-6 alkoky,
R^6 represents a substituent, and
s represents 0 or an integer of 1-4.

19. The compound according to claim 16, wherein the cyclic group optionally with a substituent(s) represented by A is



wherein R^7 represents a substituent,
R^8 represents hydrogen, or C1-6 alkyl,
R^9 represents a substituent,
t represents 0 or an integer of 1-4,
u represents 0 or an integer of 1-4, and
n represents 0 or an integer of 1-2.

20. The compound according to claim 17, wherein R^2 is hydroxy.

21. The compound according to claim 18, wherein R^4 is amino optionally with a substituent(s).

22. The compound according to claim 20, wherein R^1 is a chain substituent.

23. The compound according to claim 20, wherein R^1 is a cyclic substituent.

24. The compound according to claim 22, wherein the chain substituent is alkyl.

25. The compound according to claim 22, wherein the chain substituent is substituted alkyl.

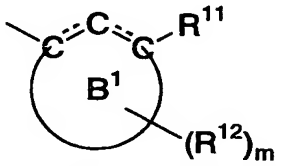
26. The compound according to claim 20, wherein R^1 is carbamoyl optionally with a substituent(s), carboxyl, alkoxycarbonyl, cyano, or acyl.

27. The compound according to claim 24, wherein the cyclic group optionally with a substituent(s) represented by B is an aromatic ring.

28. The compound according to claim 24, wherein the cyclic group optionally with a substituent(s) represented by B is a nonaromatic group.

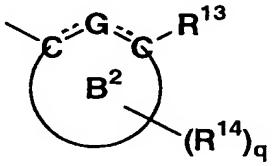
29. The compound according to claim 27, wherein the cyclic group is substituted with 1 or at least 2 substituent(s).

30. The compound according to claim 29, wherein the cyclic group with at least 2 substituents is



wherein B^1 represents a carbon ring of an aromatic ring,
R^{11} and R^{12} each represents a substituent,
m represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

31. The compound according to claim 29, wherein the heterocyclic ring with at least 2 substituents is



wherein B^2 represents a heterocyclic ring of an aromatic ring,
R^{13} and R^{14} each represents a substituent,
G represents carbon, nitrogen, oxygen, or sulfur,
q represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

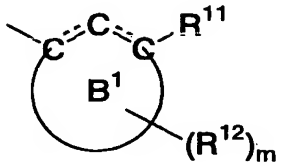
32. The compound according to claim 23, wherein the cyclic substituent is a saturated carbon ring.

33. The compound according to claim 32, wherein the cyclic group optionally with a substituent(s) represented by B is an aromatic ring.

34. The compound according to claim 32, wherein the cyclic group optionally with a substituent(s) represented by B is a nonaromatic ring.

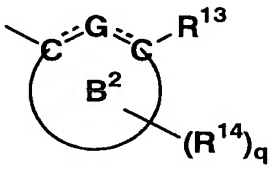
35. The compound according to claim 33, wherein the cyclic group is substituted with 1 or at least 2 substituent(s).

36. The compound according to claim 35, wherein the cyclic group with more than 2 substituent is



wherein B^1 represents a carbon ring of an aromatic ring,
R^{11} and R^{12} each represents a substituent,
m represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

37. The compound according to claim 35, wherein the heterocyclic ring with at least 2 substituents is



wherein B^2 represents a heterocyclic ring of an aromatic ring,
R^{13} and R^{14} each represents a substituent,
G represents carbon, nitrogen, oxygen, or sulfur,
q represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

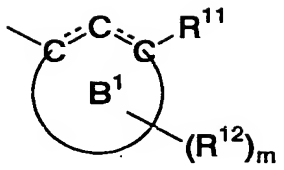
38. The compound according to claim 23, wherein the cyclic substituent is an unsaturated carbon ring.

39. The compound according to claim 38, wherein the cyclic group optionally with a substituent(s) represented by B is an aromatic ring.

40. The compound according to claim 38, wherein the cyclic group optionally with a substituent(s) represented by B is a nonaromatic ring.

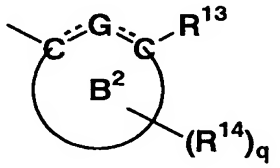
41. The compound according to claim 39, wherein the cyclic group is substituted with 1 or at least 2 substituent(s).

42. The compound according to claim 41, wherein the cyclic group with at least 2 substituents is



wherein B^1 represents a carbon ring of an aromatic ring,
R^{11} and R^{12} each represents a substituent,
m represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

43. The compound according to claim 41, wherein the heterocyclic ring with at least 2 substituents is



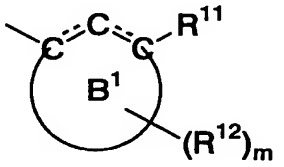
wherein B^2 represents a heterocyclic ring of an aromatic ring,
R^{13} and R^{14} each represents a substituent,
G represents carbon, nitrogen, oxygen, or sulfur,
q represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

44. The compound according to claim 14, wherein the cyclic group optionally with a substituent(s) represented by B is an aromatic ring.

45. The compound according to claim 14, wherein the cyclic group optionally with a substituent(s) represented by B is a nonaromatic ring.

46. The compound according to claim 44, wherein the cyclic group is substituted with 1 or at least 2 substituent(s).

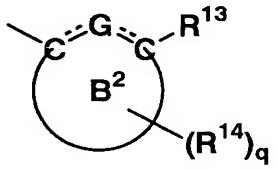
47. The compound according to claim 46, wherein the cyclic group with at least 2 substituents is



wherein B^1 represents a carbon ring of an aromatic ring,
R^{11} and R^{12} each represents a substituent

m represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

48. The compound according to claim 46, wherein the heterocyclic ring with at least 2 substituents is



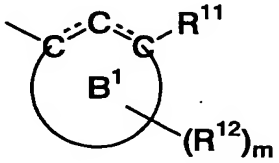
wherein B^2 represents a heterocyclic ring of an aromatic ring,
R^{13} and R^{14} each represents a substituent,
G represents carbon, nitrogen, oxygen, or sulfur,
q represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

49. The compound according to claim 25, wherein the cyclic group optionally with a substituent(s) represented by B is an aromatic ring.

50. The compound according to claim 25, wherein the cyclic group optionally with a substituent(s) represented by B is a nonaromatic ring.

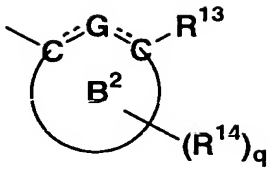
51. The compound according to claim 49, wherein the cyclic group is substituted with 1 or at least 2 substituent.

52. The compound according to claim 51, wherein the cyclic group with at least 2 substituents is



wherein B^1 represents a carbon ring of an aromatic ring,
R^{11} and R^{12} each represents a substituent,
M represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

53. The compound according to claim 51, wherein the heterocyclic ring with at least 2 substituents is

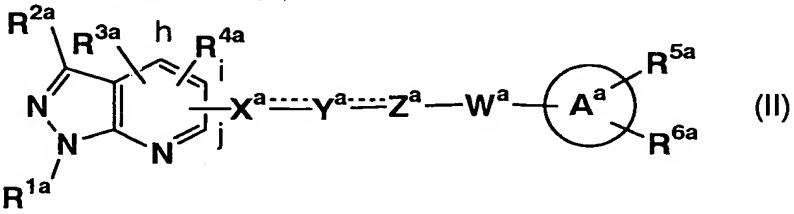


wherein B^2 represents a heterocyclic ring of an aromatic ring,
R^{13} and R^{14} each represents a substituent,
G represents carbon, nitrogen, oxygen, or sulfur.
q represents an integer of 1-4, and
the other symbols have the same meanings as those mentioned above.

54. An EDG-5 antagonist comprising the compound represented by formula (I):

$$A—X—Y—Z—B \qquad (I)$$

wherein all the symbols have the same meanings as those of claim 6, except a compound represented by formula (II):



(II)

wherein all the symbols have the same meanings as those of claim 7, or
a pharmaceutically acceptable salt thereof.

55. An EDG-5 antagonist comprising the compound according to claim 10, wherein the cyclic group optionally with a substituent(s) represented by A, or the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring (except pyrazolo[3,4-b]pyridine) containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

56. An EDG-5 antagonist comprising the compound according to claim 10, wherein the cyclic group optionally with a substituent(s) represented by A and the cyclic group optionally with a substituent(s) represented by B is a monocyclic C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

57. An EDG-5 antagonist comprising the compound according to claim 10, wherein X is a single bond and the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

58. An EDG-5 antagonist comprising the compound according to claim 10, wherein X binds to a nitrogen atom included in the cyclic group optionally with a substituent(s) represented by A and the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from 1-2 oxygen atom(s), 1-2 nitrogen atom(s), and/or 1-2 sulfur atom(s).

59. An EDG-5 antagonist comprising the compound according to claim 19.

60. A prodrug of a compound represented by formula (I):

A—X—Y—Z—B (I)

wherein all the symbols have the same meanings as those of claim 6, or
a prodrug of a pharmaceutically acceptable salt thereof.

61. A method for treatment and/or prevention of a disease due to constriction of blood vessels in a mammal, which comprises administrating to a mammal an effective dose of a compound represented by formula (I):

A—X—Y—Z—B (I)

wherein all the symbols have the same meanings as those of claim 6, or
a pharmaceutically salt thereof.

62. A method for inhibition of EDG-5 in a mammal, which comprises administering to a mammal an effective dose of the compound according to claim 10, wherein the cyclic group optionally with a substituent(s) represented by A, or the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring, except pyrazolo[3,4-b]pyridine, containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

63. A method for inhibition of EDG-5 in a mammal, which comprises administering to a mammal an effective dose of the compound according to claim 10, wherein the cyclic group optionally with a substituent(s) represented by A, or the cyclic group optionally with a substituent(s) represented by B is a C3-15 monocyclic carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

64. A method for inhibition of EDG-5 in a mammal, which comprises administering to a mammal an effective dose of the compound according to claim 10, wherein X is a single bond and the cyclic group optionally with a substituent(s) represented by B is a C3-15 monocyclic carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

65. A method for inhibition of EDG-5 in a mammal, which comprises administering to a mammal an effective dose of the compound according to claim 10, wherein X binds to a nitrogen atom included in the cyclic group optionally with a substituent(s) represented by A and the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from 1-2 oxygen atom(s), 1-2 nitrogen atom(s), and/or 1-2 sulfur atom(s).

66. Use of a compound represented by formula (I):

A—X—Y—Z—B (I)

wherein all the symbols have the same meanings as those of claim 6, or

a pharmaceutically salt thereof, for producing a therapeutic and/or preventing agent of a disease due to constriction of blood vessels.

67. Use of the compound according to claim 10, for producing an EDG-5 antagonist, wherein the cyclic group with optionally a substituent(s) represented by A, or the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring (except pyrazolo[3,4-b]pyridine) containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

68. Use of the compound according to claim 10, for producing an EDG-5 antagonist, wherein the cyclic group optionally with a substituent(s) represented by A, and the cyclic group optionally with a substituent(s) represented by B is a C3-15 monocyclic carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

69. Use of the compound according to claim 10, for producing an EDG-5 antagonist, wherein X is a single bond and the cyclic group optionally with a substituent(s) represented by B is a C3-15 monocyclic carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).

70. Use of the compound according to claim 10, for producing an EDG-5 antagonist, wherein X binds to a nitrogen atom included in the cyclic group optionally with a substituent(s) represented by A and the cyclic group optionally with a substituent(s) represented by B is a C3-15 carbon ring, or an optionally saturated or unsaturated 3-15 membered monocyclic, bicyclic, or tricyclic aromatic heterocyclic ring containing 1-5 hetero atoms selected from an oxygen atom(s), a nitrogen atom(s), and/or a sulfur atom(s).